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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER
	8

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary

Application No.	Applicant(s)
09/247,874	Duff
Examiner	**Group Art Unit**
Richard Schnizer	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-42* is/are pending in the applicat

Of the above, claim(s) *15-36* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14 and 37-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-14, and 34-42 drawn to drawn to isolated nucleic acids, methods of diagnosis, and transgenic animals comprising the nucleic acids, classified in class 536, subclass 23.1.

II. Claims 15-19, drawn to methods of treatment comprising administration of an IL-1β agonist, classified in class 514, subclass 2.

III. Claims 20 and 21, drawn to methods of establishing an IL-1β population profile, classified in class 436, subclass 94.

IV. Claims 22-27, drawn to methods of identifying compounds affecting IL-1β expression *in vitro*, classified in class 435, subclass 7.21.

V. Claims 28-30, drawn to methods of identifying compounds affecting IL-1β expression *in vivo*, classified in class 800, subclass 3.

VII. Claims 31-33, drawn to unknown compounds, classified in class 514, subclass 1.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids of group I are related to the methods of groups II-VI, because at least a portion of the nucleic acid of group I must be identified in the methods of group II-VI. The inventions are distinct because the nucleic acids of group I can be used for different purposes such as hybridization probes or for the construction of transgenic animals. The nucleic acids of group I are related to the unknown compounds of group VII because the unknown compounds modulate the expression of the gene product of the nucleic acids. The inventions are distinct because the compounds of group VII are not the nucleic acids of group I, and neither can be used to make the other. Further, these products do not have the same structure or function.

The methods of treatment of group II are related to the methods of groups III-V because these methods all require identification of the same nucleic acid. The inventions groups II and III are distinct because these methods produce different products, and neither can be used to produce the product produced by the other. Further, the products produced by the method of group II are biochemical in nature, whereas the product produced by the method of group III is purely informational.

The methods of group II are distinct from the methods of groups IV and V because the methods of groups IV and V are methods of identifying a compound whereas the method of group II is a method of treatment with an agonist. The inventions are distinct because the methods of groups IV and V do not produce an agonist *per se*. These methods could produce a compound which increases the rate of IL-1β production, but such a compound would not be correctly

classified as an agonist of IL-1β. Further, the methods of groups IV and V could produce compounds which cause a decrease in IL-1β production.

The methods group II are unrelated to the unknown compounds of group VI because the compounds of group VI could not be properly characterized as agonists, and could not be used in the methods of group II. Further the methods of group II do not result in the production of the compounds of group VI.

The methods of group III are related to the methods of group s IV and V only because identification of the same nucleic acid sequence is required to perform the methods. The inventions are unrelated because they cannot be to produce the same product. Further, the products produced by the method of groups IV and V are biochemical in nature, whereas the product produced by the method of group III is purely informational.

The methods of group III are unrelated to the unknown compounds of group VI. The methods of group III cannot be used to produce the compounds of group VI, and the unknown compounds cannot be used in the method of group III.

The methods of groups IV and V are related because they can produce the same compounds. The inventions are distinct because they use distinct method steps, and because they can be practiced completely independently of each other. The methods of group IV can be practiced with a an isolated cell or a cellular extract, whereas the methods of group V must be practiced *in vivo*.

The methods of groups IV and V are related to the unknown compounds of group VI because the methods can be used to produce the compounds. The inventions are distinct because the compound can be produced by a distinct method in which the IL-1B gene is replaced by a reporter gene, and activity of the IL-1B promoter is measured based on expression of the reporter product.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter, and because each invention requires a separate, non-coextensive search, restriction for examination purposes as indicated is proper.

During a telephone conversation with Beth Arnold on 10/4/99 a provisional election was made with traverse to prosecute the invention of group I, claims 1-14 and 34-36. Subsequent to this conversation the Examiner found that claims 37-42 could reasonably be included in this group. Affirmation of this election must be made by Applicant in replying to this office action.

Claims 15-33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-14 and 34-42 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov).

Claims 40-42 are drawn to the genus of transgenic non-human animals comprising SEQ ID NO:2 and a phenotype characteristic of inflammatory disease. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure. It is not realistic to expect that the complete structure of a transgenic animal could be described, therefore the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In this case, the specification describes phenotypic consequences, but does not provide a disclosure which enables a skilled artisan to produce any of the animals of the claimed genus (see discussion below under

Enablement). The amount of description required to convey to one of skill in the art that applicant is in possession of the claimed invention is inversely related to the predictability of the art. As discussed below, a skilled artisan cannot currently predict with certainty the phenotype of a hypothetical transgenic animal because of the array of uncontrolled variables which affect transgene expression e.g., integration site, inactivation by methylation, position effects, availability of appropriate transcription factors, etc. The instant specification does not disclose even a single working example of any species of the claimed genus of transgenic animals. In view of the unpredictability of transgenic animal phenotypes, this disclosure is insufficient to convey to one of skill in the art that applicant was in possession of the invention at the time of filing.

Enablement

Claims 1-14, and 37-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention. With respect to claims 1-14, the invention comprises methods of determining susceptibility to diseases or conditions which are caused by high levels of IL-1β, and kits for performing the methods. The methods depend on detection of a recently discovered genetic polymorphism in the IL-1β gene (IL-1B) which is associated with chronic overproduction of IL-1β. The polymorphic marker is called IL-1B allele 2 (+6912).

Breadth of the claims. The claims encompass any disease or condition caused by high levels of IL-1β, including a list of 19 specific diseases recited in claim 3.

State of the prior art. The specification and the prior art teach a *Taq I* polymorphic marker in IL-1B which is associated with chronic overproduction of IL-1β. The *Taq I* marker is very tightly linked with IL-1B allele 2 (+6912) (see Example 6 on pages 44-46 of the specification), and has been shown to correlate with periodontal disease (see Kornmann et al, US Patent 5,686,246, issued 11/1997). Duff et al, (WO 98/54359, published 12/1998) disclose that the *Taq* I marker, in combination with several other alleles of other genes in the IL-1 gene cluster (the 33221461 haplotype), is associated with periodontal disease, juvenile chronic arthritis, psoriasis, insulin-dependent diabetes, and diabetic retinopathy (see page 5, lines 11-13). Support for this disclosure is provided by reference to a variety of publications, however none of these publications is incorporated by reference into the instant specification. Further, the prior art does not establish a causal biochemical relationship between chronic IL-1β overproduction and any disease. In fact, Duff teaches that the identification of the 33221461 haplotype should "allow the investigator to begin to determine which of the alleles are causative, rather than merely linked to a disease-causing allele." See page 13, lines 16-18 of WO 98/54359. Thus at the time of the invention, no biochemical linkage between IL-1β overexpression and any disease state had been established.

Teaching and examples in the specification. The specification fails to provide any evidence which establishes a biochemical linkage between IL-1β overproduction and any specific

disease. With respect to the involvement IL-1B allele 2 (+6912) in specific inflammatory diseases, the specification asserts that the allele "probably contributes to the pathology of, at least diabetic retinopathy, periodontal disease, juvenile chronic arthritis, psoriasis, and insulin-dependent diabetes." See page 46, lines 15-17. Support for this assertion comes only by reference to other publications. See page 2, lines 10-25. However, in any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. MPEP608.01 (p). See In re Fouche , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

In light of the art-recognized lack of biochemical evidence linking overexpression of IL-1β to any disease, and the failure of the instant specification to provide such evidence, a skilled artisan would be required to perform undue experimentation in order to use the invention as claimed.

This rejection of claims 1-14 can be overcome by amending claims 1 and 6 such that they are drawn to a method or a kit for predicting an individual's susceptibility to periodontal disease, and by omitting the words "a disease or condition, which is caused by or contributed to by an inappropriately high level of IL-1β". Prediction of susceptibility to periodontal disease is considered enabled because Kornmann (US Patent 5,686,246) teaches that the Taq I marker to which IL-1B allele 2 (+6912) is tightly linked is predictive of increased risk of periodontal disease.

With respect to claims 37-39, the invention encompasses transgenic non-human animals of any species. The transgene may be expressed in any quantity, but the animal is not characterized by any phenotype which distinguishes it from any other animal.

The specification fails to teach or provide examples of how to use a transgenic animal which is not characterized by any phenotype that readily distinguishes it from a wild type version of the animal. The specification teaches that, in humans, the protein encoded by SEQ ID NO:2 is overexpressed relative to other alleles of the same gene. The specification and the prior art further establish that there is a correlation with the presence of SEQ ID NO:2 and the occurrence of periodontal disease. However, the specification fails to establish a functional linkage between expression of SEQ ID NO:2 and any disorder, and the prior art suggests that no such linkage had been established that at the time of the invention. See page 13, lines 16-18 of WO 98/54359, published 12/1998. Thus the specification has failed to establish that the presence of SEQ ID NO:2, and its expression at any level, correlate with any phenotype in any animal.

Because the claimed animals lack a distinguishing phenotype, and because the specification fails to establish that expression of the claimed transgene will result in any distinguishing phenotype, a skilled artisan would have to perform undue experimentation in order to use the invention.

With respect to claims 40-42, the invention encompasses a transgenic animal comprising SEQ ID NO:2.

Claims 40-42 encompass transgenic animals which have a phenotype characteristic of an inflammatory disorder.

The prior art teaches that the phenotype of transgenic animals is extremely difficult to predict. The level and specificity of expression of a transgene, as well as the resulting phenotype of the transgenic animal, are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g., specific promoters, presence or absence of introns, etc. The instant specification, while providing extensive information concerning how one might control certain aspects of transgene expression, does not teach what level of transgene expression is required to produce the claimed phenotype, or how to reproducibly achieve that level in any or all transgenic animals.

Furthermore transgene expression in different species of transgenic non-human animals is not predictable and can vary according to the particular host species and specific promoter/gene

combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of even one transgenic animal of the claimed phenotype, a skilled artisan would have to perform extensive experimentation to produce any transgenic animal of the claimed phenotype.

In light of the art-recognized unpredictability of transgenic animal phenotypes, particularly when considering animals of different species, and in light of the lack of guidance and examples in the specification regarding the production of the desired phenotype, a skilled artisan would have to perform undue experimentation in order to make the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-42 are indefinite because the scope of claim 34 is unclear. Claim 34 is drawn to "an isolated nucleic acid as shown in SEQ ID NO:2". This can be interpreted two ways. The nucleic acid of claim 34 either consists of SEQ ID NO: 2, or it comprises nucleotides sequences encompassed by SEQ ID NO:2. The second interpretation encompasses sequences as long as SEQ ID NO:2 and as short as a dinucleotide. If the first interpretation is employed, then claims 35 and 36 are indefinite because they are drawn simultaneously to the complete sequence of SEQ ID NO:2 and to fragments of that sequence.

Claim 35 is indefinite because it is drawn to polynucleotides of less than 6912 nucleotides in length which must contain a guanine at position 6912.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Clark et al (GenBank Accession No. X04500).

Clark teaches a genomic sequence for human prointerleukin 1 beta which is 100% identical to the sequence of SEQ ID NO:2. See enclosed sequence alignment. Thus Clark anticipates the claim.

Claims 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai et al (Cytokine 8(4): 288-293, 4/1996).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Clark et al (Nuc. Acids Res. 14(20): 7897-7914, 1986) and Clark et al (GenBank Accession No. X04500, 6/1997).

Clark (1997) teaches a genomic sequence for human prointerleukin 1 beta which is 100% identical to the sequence of SEQ ID NO:2. The sequence of nucleotides in this molecule was determined by Sanger sequencing (See Clark (1986) page 7899, first full paragraph). One of skill in the art appreciates that this technique produces a variety of nucleic acid molecules which differ in length by a single base. These molecules are separated from each other by polyacrylamide gel electrophoresis. It is well known to one of skill in the art that, at the time of the invention, a

standard sequencing gel easily resolved fragments of 100 to 200 nucleotides. Thus, on the sequencing gel in which the G residue was resolved at position 6912, there must have been polynucleotides in excess of 100 nucleotides in length which comprised the G at postion 6912, and which were separated (isolated) from other polynucleotides.

Thus Clark anticipates the claim.

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (Nuc. Acids Res. 14(20): 7897-7914, 1986) and Clark et al (GenBank Accession No. X04500, 6/1997)

Clark (1986) teaches the sequencing of the nucleic acid sequence of SEQ ID NO:2. This procedure involved subcloning restriction fragments derived from large (12-32 kilobase) segments of genomic DNA. The subcloned fragments were then subjected to progressive exonuclease digestion to generate a set of overlapping clones which were subsequently sequenced. See page 7899, first full paragraph, and Fig. 3 on page 7902. Clark (1986) does not appear to disclose the entire sequence of SEQ ID NO:2.

Clark (1997) discloses the entire sequence of SEQ ID NO:2 and cites the Clark (1986) reference.

It would have been obvious to one of ordinary skill in the art at the time of the invention to digest the DNA sequence of Clark with restriction endonucleases such that fragments of 5000-7000 bases were produced. One would have been motivated to do so because one of ordinary skill in the art appreciates that fragments of this size are easily resolved by gel electrophoresis and

are a convenient size for subcloning. The sequencing protocol of Clark involved making progressive deletions of M13 clones comprising restriction fragments derived from genomic library sequences of 12-32 kb in length (see page 7899, first full paragraph; page 7900, first full paragraph and Fig. 1; and page 7901, line 8). M13 clones containing inserts of 5000-7000 bases would be excellent substrates for progressive deletions, and would therefore facilitate DNA sequencing. Alternatively, one would have been motivated to express any fragment of the human IL-1B gene, including one encoded by a 5000-7000 base fragment, in order to raise antibodies against IL-1β.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Claims 1-14 and 40-42 are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800